EURORDIS
RARE DISEASES EUROPE

DRUG REPURPOSING: OPPORTUNITIES & CHALLENGES, A PATIENTS ' PERSPECTIVE

XVIth GIANNI BENZI FOUNDATION FORESIGHT TRAINING COURSE

DECEMBER 18TH, 2023

BARI

Learnings from past attempts: 2004, OrphanXchange

les entreprises du médicament
La recherche avance, la vie progresse
Alliance Maladies Rares
GIS Institut des maladies rares
orphanet
Inserm
Institut national de la santé et de la recherche médicale

LSSM-CT-2004-503246

Press release

July 2004

Launch of "OrphanXchange" and "Erditi": Two European pioneering initiatives to boost the development of therapies for rare diseases

At the end, only one repurposing project had emerged. Why?

- Disputes over IP rights "I thought of it first, how to protect my idea?" – complex contractual arrangements and few patent engineers / lawyers in universities
- R&D and evaluation costs, how to cover them?
  - Return on investment?
  - No reward for the institution that proposed the new use, no incentives for the evidence generation
  - To increase price? Would not work, ie substitution*
- **2023: are these resolved?**

- **OrphanXchange** (www.orphanxchange.org) seeks to promote **partnerships** between academic research projects and private companies with the aim of developing diagnostic solutions and "orphan" drugs. This exchange of information is facilitated via **OrphanXchange's database website**. **Therapy** development projects can result from academic research alone or may involve compounds that are already marketed for other indications, and which may, in turn, also be used in the treatment of rare diseases. The OrphanXchange database already contains projects for possible orphan drug indications involving **over** 50 rare diseases. The OrphanXchange **website** is (www.orpha.net). OrphanXchange, a program developed within an Inserm department, is supported by the European Commission's DG Research Framework 6 Programme and the LEEM (French Pharmaceutical Companies Association).

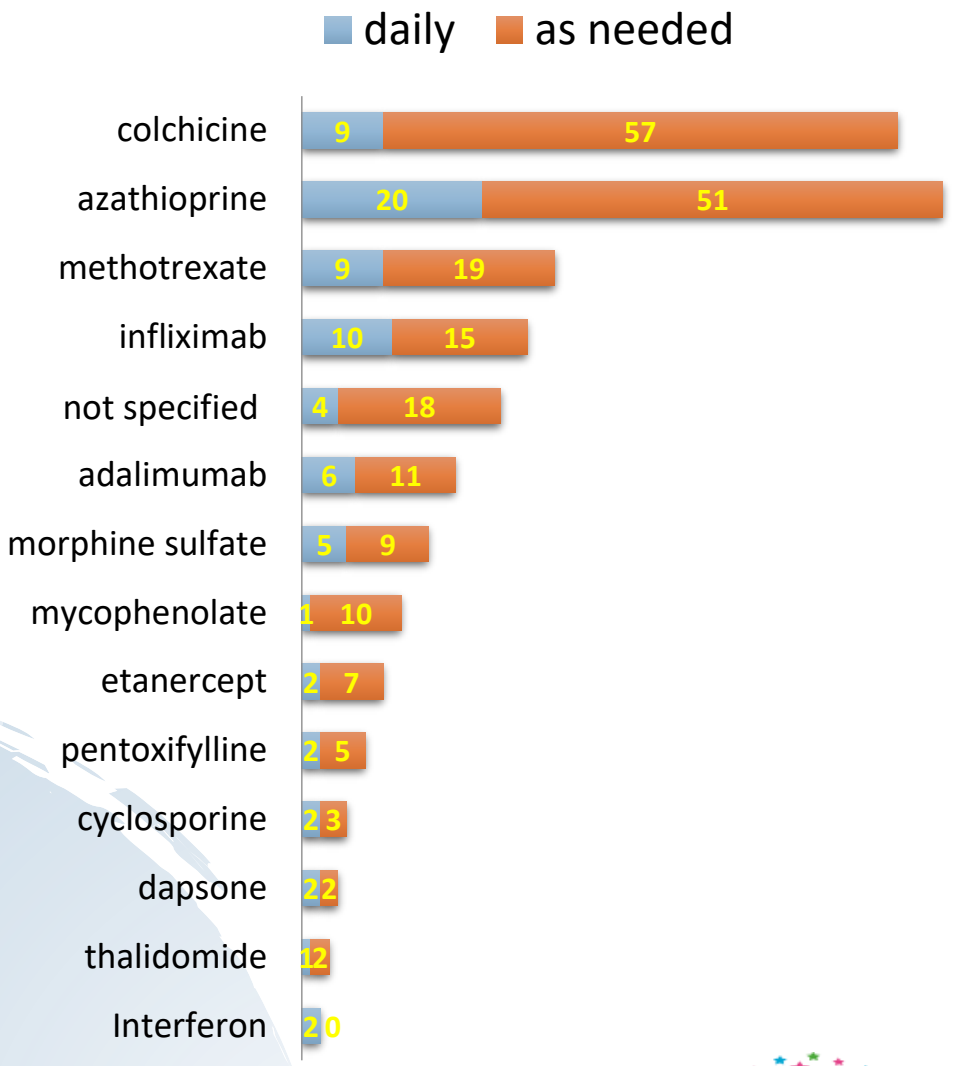
*INN prescribing mandatory as frequent measure following financial crisis 2008
Vogler S, Zimmermann N, Leopold C, Joncheere KD. *Pharmaceutical policies in European countries in response to the global financial crisis*. Southern Med Review (2011) 4;2:69-79

“I don’t find my disease in the leaflet!”

Behcet’s syndrome social network (Rareconnect) 2014

- Number off-label: all
- Number in clinical trials: 0
- Number with data collection (efficacy or safety): 0
- Yet: *patients suffering from rare conditions should be entitled to the same quality of treatment as other patients* (Recital 2 REG. EC 141/2000)

Q11 What medications are you currently taking for Behcet's syndrome?



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Drug repurposing? Patients ask for it!

Forsteo®

For **osteoporosis** (menopaused women or people with high risk of bone fractures)
Form of parathyroid hormone
Eli Lilly , authorised 2003
Sales US$ 779 mio 2008

HypoPara-Thyroidism

In children : rare condition, unmet need
Dr Karen Winer tested parathyroid hormone with some results (USA)
2007: Scandinavian groups contacted EURORDIS

Issues

Could patients with HPTH use Forsteo® off-label?
But: evidence? Does it help? At what dose? Risk to induce osteosarcoma?
Off-label not legally possible in all MS
Reimbursement of off-label not possible everywhere

EURORDIS targets

- Asked for SA to Afssaps on this new use
- Met with Eli Lilly. Obtained Eli Lilly grant CAB 2010
- To convince Eli Lilly to conduct CTs and submit a MA variation and/or post-MA monitoring

But at the end…

- Disagreement between clinicians: who thought of it first ? who should lead the work?
- Patient groups divided
- No agreement with Eli Lilly

Partnering with industry

Nick Sireau Chair of AKU Society – had a child born with AKU in 2003

EURORDIS Summer School on R&D 2011

Patient driven consortium

Obtained an Horizon 2020 research grant

€6 mio, dose ranging study – Sonia 1 study

Identified 150+ trial participants – Sonia 2

ended January 2019

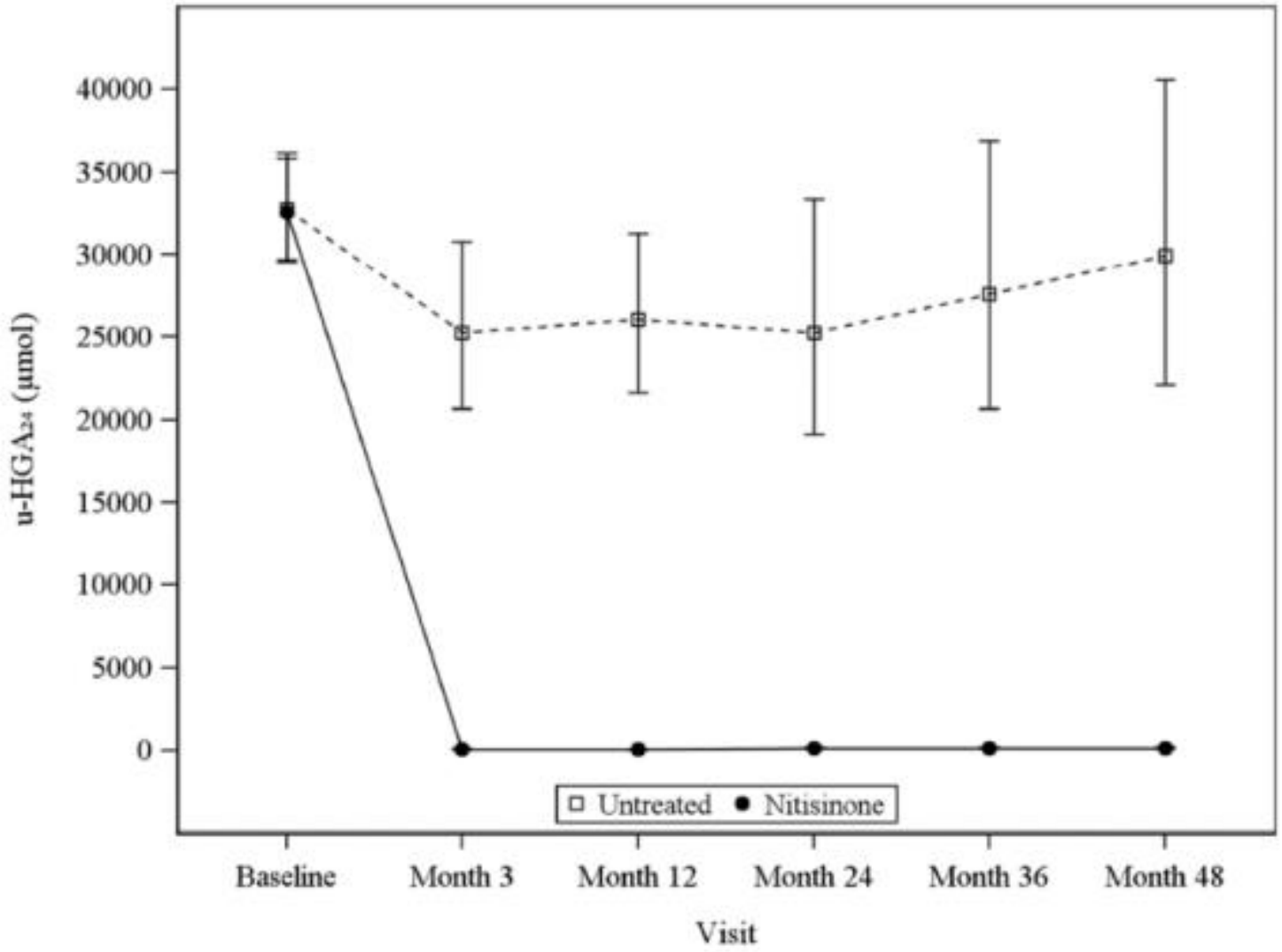
Nitisinone already used for Tyrosinemia

SOBI as industrial partner

Other producers

EMA positive opinion on extension of indication to AKU on 17/09/2020

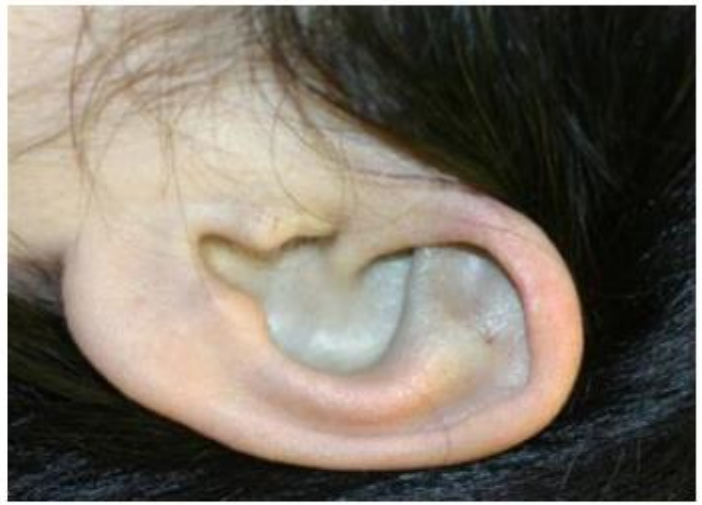
https://akusociety.org/wp-content/uploads/2020/11/ecrd-poster-2020-AKUS-08.04.20-final.pdf

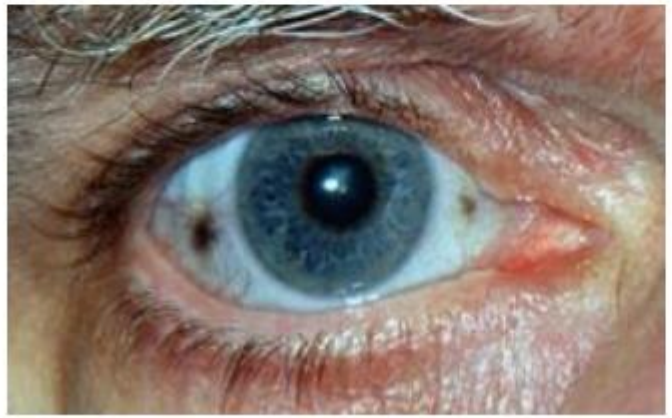


Graph shows geometric mean (95% CI) for baseline and adjusted geometric mean (95% CI) for later time points.

High circulating homogentisic acid HGA

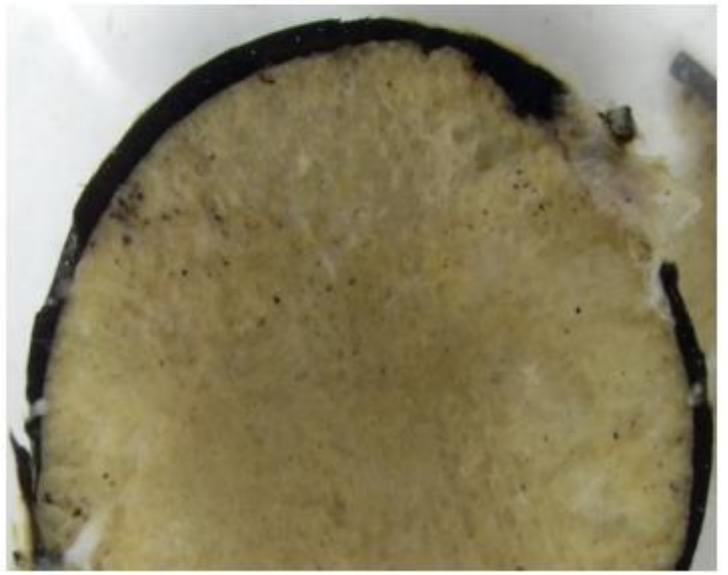
The AKU tetrad





Courtesy Nick Sireau AKU Society

Black Bone Disease

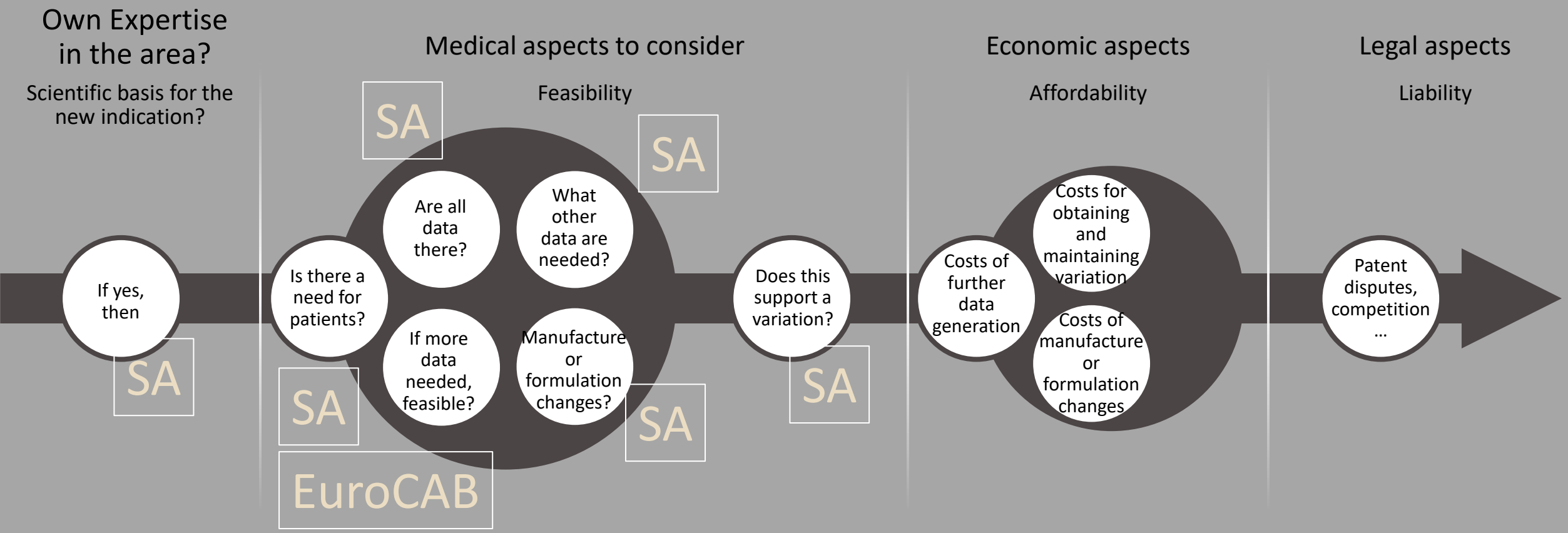


Problem statement: the market is not organised for repurposed medicine

- EMA positive opinion
  - but HGA not a surrogate marker for clinical benefit
- HTA: clinical impact not demonstrated
  - For some HTAs: clinical impact is weak, added therapeutic value is absent
  - Price should not be higher than comparators (nitisinone generics)
  - But even if it could (to recoup R&D costs), generic substitution with lower price product would occur
- MAH SOBI never planned to make profits with this indication
  - Patients in France can have access and can be reimbursed
- Is it fair to let a company demonstrate efficacy/safety for a new use (a rare disease), and let the company's competitors benefit from the research?

Issues and concerns patients have

- Price increase after new use authorised?
- Old product, can be withdrawn any time
- Industry not interested if high revenues / first use
- If off-label use well established: no RCT
- No economic model
- HTA to be consulted early
- Who pays? New funding sources? Crowdfunding, Horizon Europe?



MAH's questions. And reasons why few projects

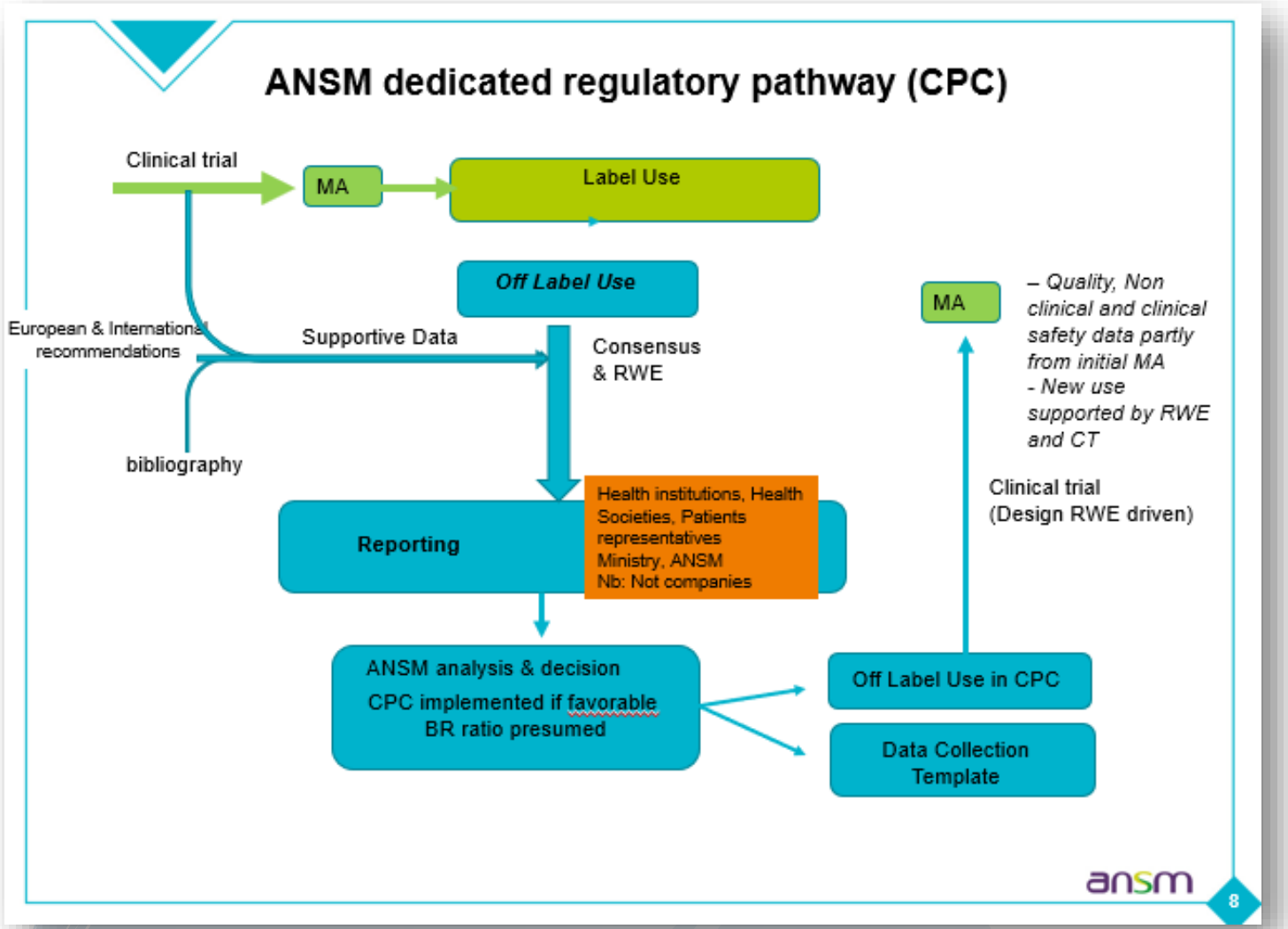
Repurposing medicines – at the same price?

An European pilot initiated by STAMP @EC
(Safe and Timely Access to Medicine for Patient)

EMA + Belgium, Spain, Sweden and Czech Rep., Finland, Germany, Hungary, Ireland, Italy

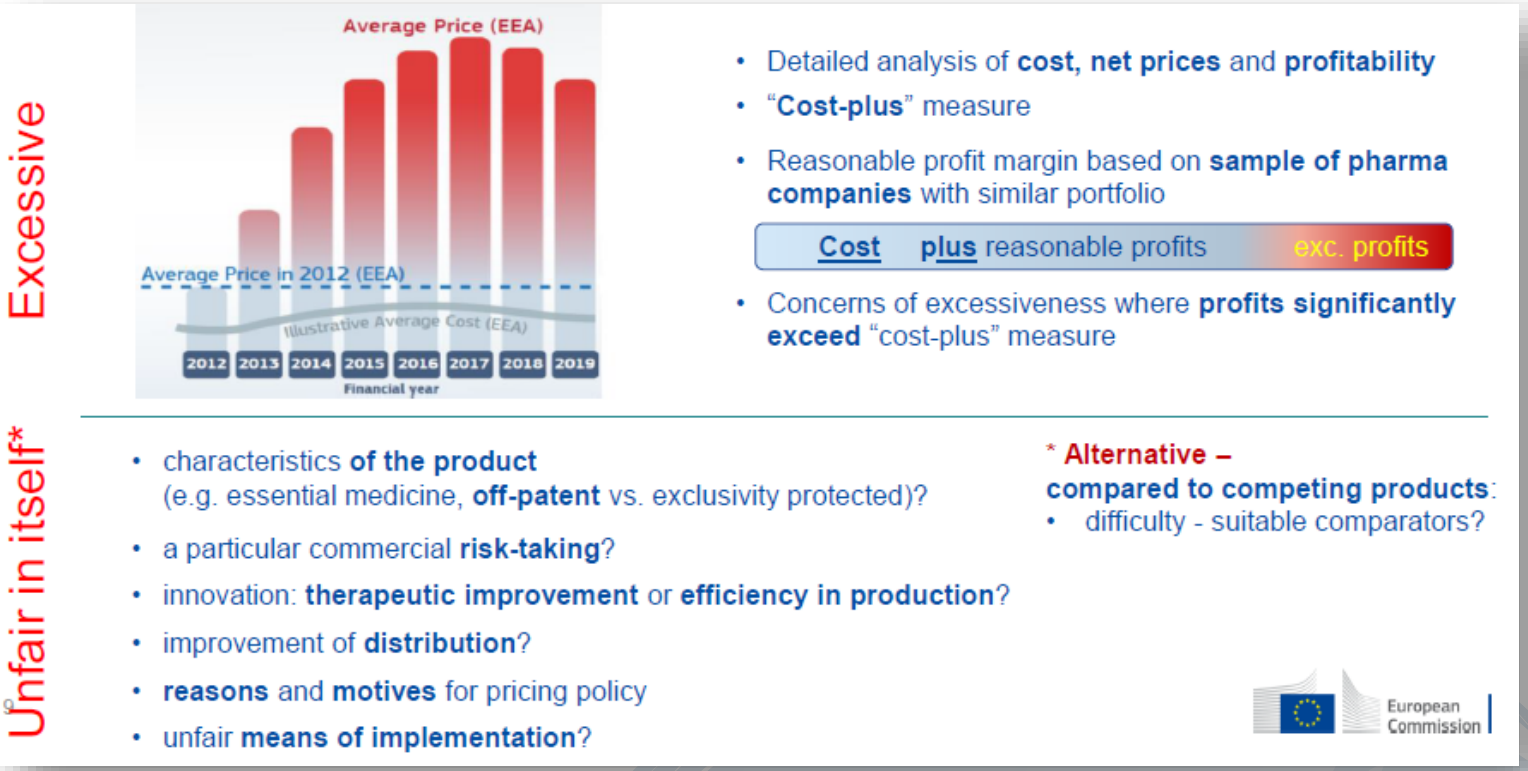
- An important role for non-profit entities “champions”
- Not for on patent / regulatory protected products
- Only if champion did not engage with industry before
  - “Anti-submarine” clause as SA fee exemption
- Repurposing advice:
  - Is evidence of high quality?
  - Is the dossier mature enough for a MAH to submit a variation?
- Public call: 28/10/2021
  - Selection: 30/06/2022
  - 35 proposals submitted, 23 representing a new indication
    - 14 SA pilots in progress
- No experience yet of champions negotiating with MAHs following advice

ANSM: Rare Diseases Observatory Survey Results 2022. 46 potential repurposing projects (CPC = regulated off-label use, proposed by clinicians and/or patients)



Curtesy Dr Valérie Denux
Head of Europe & Innovation Division

Regarding high prices: Abuse of dominant position: DG Competition and national authorities' legal tools (art. 102 Treaty)



From Anne Vernet, DG Competition, ERA
EU Law in the Pharmaceutical Sector 2023, 9 March 2023, Brussels

- See Commission's decision and method to calculate excessive profits: https://ec.europa.eu/competition/antitrust/cases/dec_docs/40394/40394_5350_5.pdf
- (EBITDA margin: measures a company's operating profit as a percentage of its revenue(Earnings Before Interest, Taxes, Depreciation, and Amortization.)
- Note: why not applied to article 8.2 of the Orphan Medicinal Products Regulation 141/2000 (Market exclusivity – Sufficient profits)?

Other points to consider

Collaboration between academics, patients and industry is needed.
Eurordis interviewed 20+vpatient groups and/or academic centres, an din a survey, identified 30+ possible repurposing projects in rare diseases. EuroCAB+++

Contradicting conclusions of the European Court Of Justice: An off-label use cannot be reimbursed if there is an authorised product (for financial considerations) and yet French Decree on Off label use for economic reasons favours off-label use accepted by CJEU

When other uses are proposed / discovered during the first use R&D, how to make sure a true R&D is in place for the second use (and not just hoping for off-label use?)

National policies/doctrines should change: if off label use and on label use can be reimbursed, but as same price than competitors, then "why bother"?

Thank you for your attention.

- François Houÿez

Director of Treatment Information and Access

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Houÿez F. High Price Medicines and Health Budgets: The Role Patients' and Consumers' Organisations Can Play. Eur J Health Law. 2020 May 18;27(3):309-323. doi: 10.1163/15718093-BJA10008. PMID: 33652398.

For repurposing pilots and/or projects: we need many types of different pilots

- First indication is for a common disease, the second for a rare one (common to rare, price unchanged)
- First indication is for a rare disease, the second for a rare one (rare to rare, price could be higher)
- First indication is for a rare disease, the second for a common one (rare to common, price can be lower)
- On patent / protected versus off patent / unprotected products versus transitioning while being repurposed
- Single source versus multi sources
- Existing data versus data to be generated (mature versus unmature)
- And also
    - Products needing structural changes (molecular level) / repurposed as they are
    - Dose change / dose unchanged
    - Administration mode change / unchanged
    - Brand Name changed / unchanged

Steps of the pilot and timelines